

Unmet clinical need in autoimmune liver diseases

Dyson, Jessica K.; Webb, Gwilym; Hirschfield, Gideon M.; Lohse, Ansgar; Beuers, Ulrich; Lindor, Keith; Jones, David E.j.

DOI:

[10.1016/j.jhep.2014.09.010](https://doi.org/10.1016/j.jhep.2014.09.010)

License:

Creative Commons: Attribution-NonCommercial-NoDerivs (CC BY-NC-ND)

Document Version

Publisher's PDF, also known as Version of record

Citation for published version (Harvard):

Dyson, JK, Webb, G, Hirschfield, GM, Lohse, A, Beuers, U, Lindor, K & Jones, DEJ 2015, 'Unmet clinical need in autoimmune liver diseases', *Journal of Hepatology*, vol. 62, no. 1, pp. 208-218.

<https://doi.org/10.1016/j.jhep.2014.09.010>

[Link to publication on Research at Birmingham portal](#)

Publisher Rights Statement:

Article subject to the terms of a Creative Commons Non-Commercial No Derivatives license.

Checked September 2015

General rights

Unless a licence is specified above, all rights (including copyright and moral rights) in this document are retained by the authors and/or the copyright holders. The express permission of the copyright holder must be obtained for any use of this material other than for purposes permitted by law.

- Users may freely distribute the URL that is used to identify this publication.
- Users may download and/or print one copy of the publication from the University of Birmingham research portal for the purpose of private study or non-commercial research.
- User may use extracts from the document in line with the concept of 'fair dealing' under the Copyright, Designs and Patents Act 1988 (?)
- Users may not further distribute the material nor use it for the purposes of commercial gain.

Where a licence is displayed above, please note the terms and conditions of the licence govern your use of this document.

When citing, please reference the published version.

Take down policy

While the University of Birmingham exercises care and attention in making items available there are rare occasions when an item has been uploaded in error or has been deemed to be commercially or otherwise sensitive.

If you believe that this is the case for this document, please contact UBIRA@lists.bham.ac.uk providing details and we will remove access to the work immediately and investigate.

Unmet clinical need in autoimmune liver diseases

Jessica K. Dyson¹, Gwilym Webb², Gideon M. Hirschfield^{2,3}, Ansgar Lohse⁴, Ulrich Beuers⁵,
Keith Lindor⁶, David E.J. Jones^{1,3,7,*}

¹Liver Unit, Freeman Hospital, Newcastle-upon-Tyne, UK; ²Centre for Liver Research and NIHR Biomedical Research Unit, University of Birmingham, UK; ³UK-PBC Research Consortium, UK; ⁴Universitat Klinikum Eppendorf, Hamburg, Germany; ⁵Department of Gastroenterology & Hepatology, Amsterdam Medical Centre, Amsterdam, Netherlands; ⁶Arizona State University Medical Centre, AZ, USA; ⁷Institute of Cellular Medicine, Newcastle University, Newcastle-upon-Tyne, UK

Summary

Despite recent advances in understanding and treatment, there remain significant areas of unmet clinical need in each of the autoimmune liver diseases (AILDs). The evolving research landscape and emerging large patient cohorts are creating unique opportunities to translate science into new therapies and care pathways, with the potential to significantly improve the lives of AILD patients. However, the areas of unmet need represent real challenges, which need to be addressed, if this vision is to be realised. This review describes the areas of unmet need in AILD in adults relating to diagnostic and prognostic assessment, primary therapy, symptom management, trial design and delivery, and structured care delivery, with the aim of focusing future research prioritisation.

© 2014 European Association for the Study of the Liver. Published by Elsevier B.V. All rights reserved.

Introduction

Autoimmune liver diseases (AILDs) are all rare diseases (defined as having a prevalence <50 per 100,000 population) but result in significant morbidity and mortality. Across primary biliary cirrhosis (PBC), autoimmune hepatitis (AIH), primary sclerosing cholangitis (PSC), and IgG4-related diseases (IgG4-RD) there

are significant areas of unmet need. Some are shared, others are disease specific (Fig. 1 and Table 1). As the research landscape in AILD evolves in parallel with high throughput genomic, proteomic, metagenomic and metabonomic platforms, the evolution of large national and international patient cohorts is being accompanied by opportunities to translate science into new therapies and care pathways. Alongside this upswing in activity, there is an opportunity to focus thoughts on the unmet needs of patients, from the initial point of accurate and timely diagnosis, to the management of end-stage liver disease and co-existent symptoms. In this review we attempt to define and delineate the areas of unmet need in AILD, which relate principally to an improvement in primary therapy, symptom management, trial design and delivery, and structured care delivery.

Key Points

- In PBC, biomarkers for high risk disease, predictive markers of UDCA non-response and secondary therapies for non-responders and/or alternative first-line therapies for patients at high risk of non-response, are needed
- A better understanding of the place of steroid therapy in overlap syndromes and for the particular role of budesonide is required
- In PSC, recognised primary therapy still does not exist and biomarkers for early stage disease, high risk patients, and enhanced cancer risks are needed
- In AIH, stratification criteria are required to enable identification of high risk patients
- In IgG4 disease, accurate diagnostic markers and evidence-based maintenance regimens are lacking
- In all AILDs, therapies are needed for the often life-changing systemic symptoms, such as pruritus and fatigue

Keywords: Unmet clinical need; Autoimmune liver diseases; Primary biliary cirrhosis; Primary sclerosing cholangitis; Autoimmune hepatitis; IgG4 disease; Stratified care delivery.

Received 19 June 2014; received in revised form 4 September 2014; accepted 5 September 2014

* Corresponding author. Address: Institute of Cellular Medicine, 4th Floor, Medical School, Newcastle University, Framlington Place, Newcastle upon Tyne NE2 4HH, UK. Tel.: +44 (0) 191 208 8696; fax: +44 (0) 191 222 0723.

E-mail address: david.jones@ncl.ac.uk (D.E.J. Jones).

Abbreviations: AILD, autoimmune liver disease; PBC, primary biliary cirrhosis; AIH, autoimmune hepatitis; PSC, primary sclerosing cholangitis; UDCA, ursodeoxycholic acid; OCA, obeticholic acid; HCV, hepatitis C virus; ALP, alkaline phosphatase; APRI, aspartate transaminase to platelet ratio; DMARDs, disease modifying anti-rheumatic drugs; DILI, drug-induced liver injury; AMA, anti-mitochondrial antibody; LPA, lysophosphatidic acid; ASBTi, apical sodium-dependent bile acid transporter inhibitor; MARS, molecular adsorbent recirculating system; HCC, hepatocellular carcinoma.



ELSEVIER

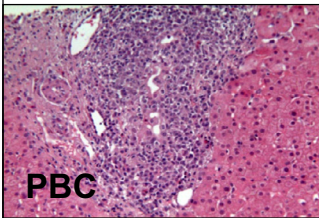
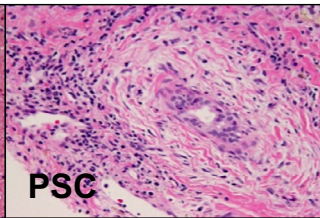
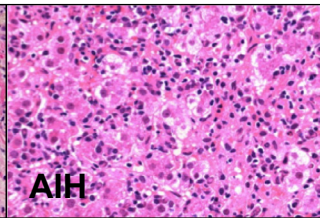
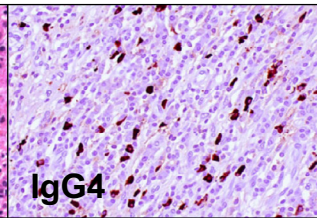
Disease modification			
New science	New drugs	New endpoints	
<ul style="list-style-type: none"> • Proteomics • Metabolomics • Genomics and metagenomics • Microbiomics • T-cell receptor sequencing • Improved disease models • Novel antigen discovery 	<ul style="list-style-type: none"> • UDCA derivatives e.g., nor-UDCA • Better options in treatment non-response (AIH, PBC) • Anti-neoplastic agents (PSC) • Steroid-sparing agents (AIH, IgG4) • Preventative and early disease-modifying options • Better evidence for old drugs e.g., fibrates 	<ul style="list-style-type: none"> • Early response criteria (PBC) • Predicting cancer risk (PSC) • Predicting treatment non-response (AIH, PBC) • Non-invasive prediction of cirrhosis (PBC, PSC) • Predicting post-transplant recurrence (all) 	
			
Symptoms and care delivery			
Itch	Fatigue	Care delivery	
<ul style="list-style-type: none"> • Improved anti-pruritics (e.g., ASBTi, anti-autotaxin) (PBC, PSC) • Itch GWAS (PBC) • Isolating causative mechanisms • Evidence base for expensive therapies e.g., MARS, nasobiliary drainage 	<ul style="list-style-type: none"> • Identify biological correlates • Explaining symptom variations • Symptom measurement • Novel agents (e.g., Rituximab in PBC) • Strengthening evidence base for existing treatments 	<ul style="list-style-type: none"> • Standardising basic therapy and diagnostic criteria (all, especially IgG4) • Reducing corticosteroid side-effects (AIH, IgG4) • Remote, patient-directed, shared primary care and stratified follow-up (all, especially PBC) 	

Fig. 1. Summary of unmet needs in autoimmune liver disease. Conditions in brackets following bullet points denote areas of particular need (PBC, primary biliary cirrhosis; PSC, primary sclerosing cholangitis; AIH, autoimmune hepatitis; IgG4, immunoglobulin G subclass 4 associated disease). Central panels show typical histological findings on haematoxylin and eosin stained liver sections (PBC, PSC, and AIH) or haematoxylin with anti-IgG4 secondary staining (IgG4). UDCA, ursodeoxycholic acid; ASBTi, apical sodium-dependent bile transport inhibitors.

Challenges in diagnosis and prognosis

In PBC, a key challenge in the area of diagnosis is the significance of anti-mitochondrial antibodies (AMA, or anti-M2 detected by ELISA) detected in the absence of liver biochemical abnormality. Early studies, performed on a cohort of 29 patients who underwent liver biopsy assessment, suggested that the majority of such AMA-positive patients with normal liver function tests (LFTs) had histological features of mild PBC (83%), and the majority went on to develop characteristic biochemical abnormalities (83%) or symptoms of PBC (76%) over a prolonged follow-up. None, however, became cirrhotic or died of the complications of PBC [1]. More recent population-based studies have suggested a prevalence for AMA in the normal population of 0.1–1% [2–4] with up to half of the AMA-positive subjects in the larger cohorts having biochemical abnormality. Long-term natural history studies are required, with baseline evaluation of the population, to identify processes and markers, associated with the subsequent development of clinically significant PBC. This will enable identification of the subgroup with enhanced risk of disease development and potential preventative approaches able to change the natural history.

In both PBC and PSC, specific questions arise with regard to the issue of so-called “overlap syndromes” with AIH and their diagnosis; a key question if specific therapy is to be considered [5–7]. Each disease naturally encompasses a heterogeneous group of patients with variations in the classical clinical, biochemical, serological, and histological findings, which can lead to difficulties in diagnosis. The classical features of AIH are elevated aminotransferases, raised IgG, positive auto-antibodies [8], and interface hepatitis with portal plasma cell infiltrate on biopsy [9]. The histology findings, however, are not specific for the diagnosis of AIH and the International Autoimmune Hepatitis Group (IAIHG) states that a diagnosis of AIH should not be made when definite bile duct pathology or granulomas are present [10]. Czaja *et al.* found that 24% of patients with “classical AIH” had biliary changes on biopsy, including destructive cholangitis, ductopenia, and non-destructive cholangitis [11] but concluded on further investigation that these patients lacked the features of PBC [12]. Conversely, the “florid duct lesion”, classically found in PBC, is not always present and granulomatous cholangitis was seen in only 32% of PBC patients in one study [13]. In PSC, the classical histology findings are portal tract inflammation with lymphocytic infiltration in the bile ducts and ductular

Table 1. Remaining challenges in autoimmune liver disease.

Disease	Challenges in diagnosis and prognosis	Challenges in therapy	Challenges in prevention	Challenges in symptom management	Challenges in trial design	Challenges in care delivery
PBC	<ul style="list-style-type: none"> • Biomarkers for high risk disease at diagnosis • Predictive markers of response to UDCA applicable early in treatment • Markers/models to indicate steroid or other immune therapy (over-lap/cross-over) 	<ul style="list-style-type: none"> • Secondary therapy for UDCA non-responders • Early immunotherapy to change disease natural history • Preventative therapy in at risk individuals (e.g., post-transplant recurrence) • Understanding the place of steroid therapy (over-lap/cross-over) 	<ul style="list-style-type: none"> • Recurrent disease post-transplant • Primary prevention in high risk individuals (AMA +ve with normal LFT, first degree relatives, etc) 	<ul style="list-style-type: none"> • Resistant pruritus • Fatigue • Cognitive impairment 	<ul style="list-style-type: none"> • Consensus stratification protocols to identify high risk patients for second line therapy trial • Surrogate outcome measures acceptable to regulatory bodies 	<ul style="list-style-type: none"> • Implementation of stratification criteria in practice enabling identification of high risk patients • Management location and approach for low risk patients
PSC	<ul style="list-style-type: none"> • Biomarkers for high risk disease at diagnosis • Biomarkers for enhanced risk of cholangio-carcinoma development 	<ul style="list-style-type: none"> • Effective primary therapy • Rationalised therapy for extra-hepatic stricture • Preventative therapy to reduce risk of cholangio- and colonic carcinoma • Preventative therapy in at risk individuals (eg post-transplant recurrence) 	<ul style="list-style-type: none"> • Recurrent disease post-transplant • Primary prevention in high risk individuals (IBD) 	<ul style="list-style-type: none"> • Resistant pruritus • Fatigue 	<ul style="list-style-type: none"> • Complexity of PSC types (extra- vs. intra-hepatic) and stratification criteria • Surrogate outcome measures acceptable to regulatory bodies 	<ul style="list-style-type: none"> • Lack of primary therapy • Approach to and delivery of screening for malignancy • Management location
IgG4 disease	<ul style="list-style-type: none"> • Specific diagnostic markers 	<ul style="list-style-type: none"> • Evidence-based primary therapy regimens • Evidence-based maintenance regimens 		Poorly defined	<ul style="list-style-type: none"> • Consensus for trial design • Surrogate outcome measures acceptable to regulatory bodies 	<ul style="list-style-type: none"> • Reach for diagnostic activity (effectiveness of diagnosis) • Management location
AIH	<ul style="list-style-type: none"> • Biomarkers for high risk disease at diagnosis • Improved response markers as surrogates for biopsy 	<ul style="list-style-type: none"> • Second-line treatment regimes for non-/partially steroid responding patients • Steroid free regimens for steroid intolerant patients 	<ul style="list-style-type: none"> • Recurrent disease post-transplant 	Poorly defined	<ul style="list-style-type: none"> • Stratification criteria • Surrogate outcome measures acceptable to regulatory bodies 	<ul style="list-style-type: none"> • Implementation of stratification criteria in practice enabling identification of high risk patients • Management location

proliferation [14]. However, interface hepatitis is sometimes seen and in one study, 33% of PSC cases had histological features similar to AIH [15]. In a potentially confusing diagnostic area, the complete clinical picture must be considered and the IAIHG suggests that patients should be categorized according to the predominant disease, with “overlap syndromes” not being considered as distinct diagnostic entities [7].

In terms of prognosis in PBC, the key challenge is the development of clinical tools/markers, able to predict the risk of non-response to ursodeoxycholic acid (UDCA), the only licensed therapy for the condition, and the need for alternative therapy approaches. Current UDCA-response assessment paradigms in PBC rely on a minimum of one year of therapy with UDCA at adequate dose. This has the effect of leaving high-risk patients, who have little chance of response, on a failing therapy for a potentially excessive time period. Advances in the field of therapy for hepatitis C (HCV) were aided by the development of early response and non-response criteria, allowing patients and clinicians to readily understand an individual patient's likelihood of treatment success, but also rapidly “triaging” patients according to their need for new therapies. Prospective studies in high-risk PBC patient populations are needed to evaluate the utility of early and interim biochemical markers and other assessments in predicting eventual response. This will facilitate the earlier stratification of patients for UDCA-response and need for second-line therapy. The very large-scale research platforms, such as the UK PBC national patient cohort, combine baseline assessment of large cohorts of patients, including significant numbers of high risk patients, and banking of key biological materials, with long-term outcomes follow-up. This will allow both assessment of key biological processes at play in patients who subsequently fail to respond to UDCA and the biomarkers to allow their effective identification [16]. The findings from the trials of budesonide therapy in PBC, amongst others, suggested that some histological features, present at disease outset, such as inflammatory grade, may be predictive of response to budesonide/UDCA combination and provide a pointer to the potential value of histological markers of subsequent treatment response; further studies are needed in this area.

The issues relating to risk stratification are more marked in PSC than in PBC, given the current lack of any validated tools or markers. However, there is some evidence emerging to suggest value in the concept of alkaline phosphatase (ALP) “response” akin to that now established in PBC (a finding, which potentially may also help clarify the future role of UDCA) [17]. There is a need to both track PSC immunologically more precisely over time, and to engender patients' willingness and clinical insight, to allow early disease intervention. This may need to be in place many years (perhaps even decades) prior to advanced disease, and the present need for transplantation. Histology may hold clues for disease management, even if it does not offer diagnostic advantage to patients. PSC exhibits added complexity when compared to PBC, with unmet clinical need particularly relating to extra-hepatic disease and the risk of colonic and cholangiocarcinoma [18]. There is a need for increased knowledge, regarding the factors pre-disposing to colonic- and cholangio-carcinoma. We need to utilize that knowledge to develop risk prediction markers to facilitate the effective management of at-risk patients, using currently typically surgical approaches. Improved understanding of the science of carcinogenesis in PSC, and the capacity to identify at-risk individuals, may enable the future

development of chemo-prevention strategies to reduce individual risk, or at the very least allow identification of high-risk patients in whom timely liver transplantation can be considered. At present, standard clinical practice is based around CA19-9 measurement, conventional radiological assessment and/or cytological assessment of bile duct brushings [19]. The α 1-4 fucosyltransferase (*FUT3*) and α 1-2 4 fucosyltransferase (*FUT2*) genes determine the Lewis phenotype of patients (Lewis antigens are components of exocrine epithelial secretions present on erythrocyte membranes) [20,21]. In Caucasians, 7–10% of individuals lack functional *FUT3* and are unable to synthesize CA19-9 (compared with 22% of the African populations), potentially giving false negative results [21,22]. Those, who lack functional *FUT2* have a non-secretor phenotype and have higher levels of CA19-9 in serum and urine, potentially giving false positive results [23]. CA19-9 can also be elevated in benign pancreatic diseases [24], including in cholestatic diseases [25]. These factors make the use of CA19-9 as a screening tool for malignancy difficult in clinical practice. There has also been some work looking at markers in urine for the development of cholangiocarcinoma, which may hold promise as non-invasive tools for screening. Metzger *et al.* have utilized a urine peptide marker model to distinguish cholangiocarcinoma from PSC and benign biliary disorders with a good accuracy (AUROC 0.87, 95% CI 0.80–0.92, $p = 0.0001$, 83% sensitivity, 79% specificity) [26]. Molecular pathology approaches, including fluorescent in situ hybridisation (FISH) of cytological specimens for the presence of polysomy, and lipidomics assessment of bile are amongst the other technologies offering real promise [27,28]. However, prospective evaluation and validation of diagnostic accuracy are required before they are recommended for routine clinical use.

There are ongoing difficulties with diagnosing AIH, and defining the disease biologically, in terms of who has a complete or incomplete treatment response. The IAIHG diagnostic criteria for AIH are useful for research purposes, but are cumbersome for routine clinical practice and may under-diagnose patients with disease variants, which may still be responsive to therapy [10]. Histology is key but at present morphologic appearances of AIH cannot readily be distinguished from viral or drug-induced liver injury (DILI). For the smaller cohort of AIH patients at risk of ultimately requiring liver transplantation, clearer early stratification of need for more intense therapy remains important to define. Adverse outcomes are more likely in patients presenting at younger ages (especially type 2 disease) and those with incomplete biochemical response, and subsequent disease flare-ups [29].

IgG4-RD was first recognized in 2001 [30] and is characterized by a dense lymphoplasmacytic infiltrate, storiform fibrosis and obliterative phlebitis [31]. Elevated serum IgG4 levels are often present [30] but are normal in up to 40% of patients with biopsy-proven IgG4-related disease [32]. IgG4-RD can affect the biliary tree causing sclerosing cholangitis. In this relatively newly appreciated disease, diagnosis can be challenging and requires the combined presence of the characteristic histopathological appearances and increased numbers of IgG4 positive plasma cells [33]. Clarification of the interrelationship between PSC and IgG4 disease is required [34]. A recently described algorithm, based on the ratio of serum IgG4 to IgG1 has shown utility for the differential diagnosis of IgG4 disease and PSC [35]. However, this approach requires independent validation and at present there are no predictive markers of outcome to reliably stratify therapy

Review

needs. The recent finding that highly expanded IgG4+ B cell clones dominate the B cell receptor repertoire in patients with IgG4-RD, and not in healthy or disease control patients, including PSC, suggests that an antigen-mediated immune response is pivotal in the pathogenesis of IgG4 associated cholangitis (IAC) and may be critical for the development of an accurate diagnostic marker of IgG4-RD [36].

Challenges in therapy

For a significant number of patients with AIH, PBC, and IgG4-RD, effective, albeit inexact, primary therapy exists [37]. PSC patients, however, lack any proven effective medical therapy [37]. Across AILDs, different groups of patients need better primary treatment, with fewer side effects, and a significant number of patients need early stratification to novel second-line therapies. Included among these groups are patients who are likely over-treated, who need better recognition as having milder, more treatment responsive disease, and in whom care can be stepped down, increasing cost-effectiveness of the disease management.

In PBC, it is now widely accepted that the majority of patients have a form of the disease, which is treated effectively by primary therapy with ursodeoxycholic acid (UDCA) at 13–15 mg/kg/day [2]. For the minority who do not respond to UDCA there is a need to understand how UDCA works and, furthermore, what UDCA “treatment failure” means biologically and clinically. While UDCA is clearly the treatment at the outset of PBC, the mechanisms of treatment failure may define substrata of PBC phenotypes with inherently different natural histories. For example, we already recognize that ductopenia and late-stage disease modify the response [16,38]. The key area of therapy need in PBC, therefore, is the development of effective alternative or second-line therapies for the significant minority of patients who either have proven UDCA under- or non-responsive forms of the disease [16,39–42], or could be predicted through baseline characteristics to be at high risk of non-responding. We also need the clinical tools with which to target those therapies effectively in practice. Currently, clinical trials of second-line agents for PBC generally require proven failure of UDCA as an entry criterion, meaning that the “reach” of UDCA primary therapy is critical [43,44].

A number of agents are currently under evaluation for the second-line treatment of PBC. These divide broadly into those targeting cholestasis and bile acid biology, and those targeting upstream autoimmune processes, although this may represent an over-simplification. The bile acid-based farnesoid X receptor (FXR) agonist obeticholic acid (OCA) has recently completed phase 2 and 3 evaluation [43,45]. There is also emerging evidence to build on earlier anecdotal findings, supporting efficacy of the fibrates (bezafibrate and fenofibrate); agents, which are already becoming widely used in some countries, notably Japan, despite their limited formal trial evidence (particularly with regard to hard clinical end points) [44,46–48]. In the context of modifying the immune response there are also data to support the use of budesonide; a glucocorticoid with high first-pass metabolism in the liver. A small study, using budesonide as add-on therapy in patients with incomplete response to UDCA showed marginal improvement in biochemistry but significant worsening of osteoporosis [49]. Other studies, combining budesonide with UDCA (without stratification for UDCA-response) compared to UDCA

alone, showed an improvement in liver histology with combination therapy [50,51]. Combination therapy led to an improvement in the disease stage of patients with higher degrees of inflammation. The mechanism of action of budesonide may be more complex than its simple immunomodulatory effects, with emerging evidence to suggest that it may play a role in restoring the “bicarbonate umbrella”, the disruption of which is thought to be integral to cholestatic bile duct injury [52]. It must be remembered that budesonide should not be used in cirrhotic patients, or those with peri-hepatic shunting, because of the high risk of side effects in patients not protected by effective first-pass metabolism.

Treatment paradigms in other autoimmune diseases, such as rheumatoid arthritis, have rapidly evolved to include the use of disease modifying anti-rheumatic drugs (DMARDs) in the earliest, overtly immunological phases of disease. Trials of biological agents in PBC have proven to be disappointing thus far [53], potentially due to targeting patients with UDCA-failure who are perhaps already within an overtly cholestatic “downstream” phase of the disease. The potential for the DMARD-type approach for the primary treatment of PBC remains largely unexplored. There is a risk that the fundamental insights gained from genomic and immunologic studies [54,55] will not be therapeutically harnessed if additional ways of stratifying risk and biologic stage of disease, as well as effective treatment, are not developed.

In PSC, the development and evaluation of an effective primary therapy is manifestly a high priority. The use of UDCA is not recommended in relevant treatment guidelines because of negative trial data relating to hard clinical end points, however, the field has been hampered by small-scale trials, the majority of which have been under-powered. Furthermore, there is clear evidence that UDCA in PSC, as is the case with PBC, has significant impact on key biological processes and serum biochemistry [56,57]. Some clinicians feel that there may be a role for careful use of UDCA in patients with well-compensated disease [58] but we must not ignore that the therapeutic trials of high-dose UDCA showed biochemical improvement but ultimately demonstrated patient harm [59]. The contrasting data pose the question as to whether there may be an optimal dose above the levels conventionally used in PBC, but below those associated with toxicity, which may open the way for effective use of UDCA in PSC [56]. A further potential area of therapeutic opportunity in PSC would be application of second-line bile acid-related therapies currently undergoing evaluation in PBC. However, important pathophysiologic differences between PBC and PSC need to be recognized, particularly bile duct obstruction and malignancy [60]. As with PBC, the adoption of a biologic-based approach to treatments, instead of, or in parallel to bile acid-based therapies, would necessitate an ability to select patients at appropriate junctures of their disease. The classic PSC phenotype of a Caucasian male in his 40s with devastating disease is increasingly challenged by large cohort studies expanding the disease spectrum across severity, gender and age. The close association with inflammatory bowel disease implies that biologic-based therapy does have merit. In terms of extra-hepatic disease in PSC there is a need for evidence-based therapies for the management of dominant strictures, where there is currently clinical uncertainty as to the relative utility of stenting and dilation therapy [60].

For IgG4-RD, most information regarding treatment is from autoimmune pancreatitis (AIP) and current approaches are often adapted from those used in AIH and may be sub-optimal. Most

patients with IgG4-RD do respond rapidly to steroid treatment but the dose and duration of therapy are unclear, as is the need for maintenance therapy [34,61]. As our experience of managing IgG4-RD increases, the need for steroid-sparing agents is likely to become clear.

As regards primary therapy in AIH, the challenges faced are not the availability of seemingly effective therapies but their use in practice. Outcomes are more disappointing than might be anticipated given the apparent efficacy of treatment [62]. Effective and evidence-based second-line therapies are needed for patients unresponsive to, intolerant of, or non-adherent with steroid-based primary immunosuppressive therapy. Steroid-free regimens are particularly important given that one potential explanation for the contrast between trial data and long-term follow-up cohort outcomes in AIH may be poor adherence to steroid-based regimes because of issues of patient acceptability [63]. Younger patients often find prednisolone therapy difficult to tolerate because of weight gain and cosmetic side effects. A sensitive and realistic approach to this issue is needed to ensure the best long-term outcomes for patients [63]. Part of the solution is through the structure of care delivery, but the development of steroid-free, or at least overtly steroid-minimising, regimes would be of significant use in appropriate patients. Budesonide has been suggested as an alternative treatment strategy in AIH due to the lower systemic steroid exposure associated with it as compared to prednisolone. In a recent trial of budesonide (9 mg/day) vs. prednisolone (40 mg/day, tapered to 10 mg/day) in selected pre-cirrhotic patients, all of whom also received azathioprine treatment, the primary end point (complete biochemical remission without steroid-specific side effects) was achieved in 47% of patients given budesonide vs. 18.4% given prednisolone ($p < 0.001$). In the budesonide group, 72% did not develop steroid side effects (vs. 46.6% with prednisolone, $p < 0.001$) [64]. These benefits and their generalizability need further clarification and the question as to whether budesonide has a role as primary therapy in AIH or is best considered as an alternative therapy in patients experiencing, or at risk of experiencing steroid side effects is an open one.

As yet, there is no consensus as to what defines a clear treatment failure in AIH by reflection of the syndromic nature of AIH, its diagnosis, and its relatively rare nature. We lack sufficiently large AIH treatment centres, able to identify and escalate therapy in a trial context, for a small but significant group of frequently young patients. Approaches to optimize the efficacy and tolerability of existing seemingly effective therapies, such as azathioprine, where underdosing/fear of side effects leads to non-optimal use, may also hold utility but require wider access to pharmacologic monitoring.

For the management of patients with overlapping features of AILD (typically PBC or PSC with features of AIH) a key question is when, if ever, the use of steroids and subsequent steroid-sparing agent regimes should be considered? The advent of UDCA non-response assessment for PBC stratification, and the use of emerging second-line therapies, directed at the cholestatic disease phase, have left the question when the targeted use of steroids should take place. A systematic approach, with prospective studies to understand the pathophysiology of overlap and define the histological, serological and biochemical criteria, suggestive of a likely steroid response, is required. Additionally, better appreciation of the effects of age on the presentation of all AILDs is needed, as an alternative viewpoint for overlap presentations

[16]. This is exemplified by the pattern of injury in children with AIH ("autoimmune sclerosing cholangitis"), which is characterized by hepatitic immune injury and the apparent impact of age, as well as gender, on the UDCA-response in PBC [6,16].

The informed development, evaluation and optimal implementation of improved primary and second-line therapies in AILD ultimately requires increased understanding of the pathophysiology of the diseases. There is a need for more human tissue-based research to demonstrate relevant mechanistic pathways, and their activation or suppression, *in vivo*. The contradictory findings in murine models and human disease in PBC with, for example regard to B cell depleting therapy [65,66], suggest that using optimized human disease-based approaches is likely more productive for effective therapy design than attempts to exploit inexact models, which have yielded little in terms of therapeutic advance. In PBC and PSC, there is a need to understand the pathophysiology of disease evolution, and the interrelationship between the apparently autoimmune early disease stage and subsequent cholestatic and fibrotic phases to allow effective targeting of second-line therapies in a timely fashion [67].

Development of preventative strategies

At present, the concept of disease prevention in AILD does not have any significant clinical traction, although we believe there may be important clinical opportunities. The most obvious area of unmet need with regard to disease prevention is avoidance of disease recurrence following liver transplantation [68]. In PBC, up to 30% of patients show features suggestive of recurrence within 5 years of transplantation [69,70]. Retrospective data suggest an association with tacrolimus-based primary immunosuppression but there are no trial data and this knowledge has not had any widespread impact on clinical practice [69]. At present there is no systematic approach to reduce the risk of PBC recurrence whether through the modification of primary immunosuppressive regimes or through prophylactic use of agents such as UDCA, used in the primary therapy of PBC. Trials are needed in this area as long-term follow-up has suggested that the development of recurrent disease is not the uniformly benign clinical event it was previously thought to be; a small group of patients run into significant clinical problems [71]. In both PSC and AIH, recurrent disease can mirror primary disease. Graft loss due to recurrence is a growing problem in PSC and the need for high levels of immunosuppression to control the highly inflammatory process seen in some patients can lead to significant morbidity [70,72]. At present, there is no systematic approach to prevent recurrence and there are no clinical trials either under way or planned. Alongside this are even more basic questions around transplant practice in PSC, such as the nature of the biliary anastomosis.

A further opportunity for disease prevention in PBC comes from the identification of high-risk individuals (such as first degree relatives of PBC patients and people who are anti-mitochondrial antibody (AMA) positive but do not exhibit overt disease) [1,73]. The prevalence of AMA-positivity in first-degree relatives of PBC patients is 13.1%, compared with 1% in controls matched for age, sex, race and residence [74]. There is, at least potentially, the opportunity to modify the disease process before it becomes established. Future prevention strategies may include avoidance of environmental triggers, identified in emerging

Review

toxicological and epidemiological research programmes [75,76]. There are also modifiable risk factors, which appear to be related to PBC. Smoking has been found to be a risk factor for the development of PBC [77]. Corpechot *et al.* found that each pack-year of increase in smoking intensity was associated with a 5.0% (95% CI, 1.3–8.7%) increased likelihood of advanced fibrosis [78]. Higher lifetime tobacco consumption (greater than or equal to 10 pack-years) is also associated with stage 3 or 4 fibrosis [79]. Based on the strength of the associations the authors believe that PBC patients, and those at risk of developing PBC (first degree relatives, AMA-positive individuals with normal liver biochemistry and PBC patients at the point of liver transplantation) should be advised to avoid smoking to reduce their PBC-related risk (in addition to the other health benefits). Previous urinary tract infections (UTI) have also been identified as a risk factor for PBC (adjusted odds ratio [AOR] 1.511, 95% CI 1.192–1.915) in a questionnaire-based case-control study of 1032 patients with PBC [80]. A case-control study in general practice also found that PBC is associated with UTI prior to diagnosis (OR 1.50 [CI 1.26–1.78]) with the strongest relationship being seen in patients under 55 years with pyelonephritis in the 5 years preceding diagnosis (AOR 2.60, 95% CI 1.02–6.63) [81]. A recent meta-analysis found the pooled OR for PBC and smoking to be 1.67 (95% CI = 1.41–1.92) and 2.02 (95% CI = 1.40–2.65) for previous UTI [82]. Whilst most pertinent to PBC, familial risk and prevention of AIH, PSC, and associated autoimmune disease is equally relevant.

Symptom management

The quality of life of patients with AILD is frequently significantly impaired [83–85]. The presence of advanced disease is specifically associated with systemic symptoms, but the majority of such impairment occurs in patients with earlier stage disease [16]. In PBC, this impairment is usually unresponsive to conventional disease therapies.

The classical PBC, PSC, and IgG4-RD cholestatic symptom is pruritus which, if severe, can have a dramatic impact on the quality of life [86]. Relief of bile duct obstruction, if present, is the first-line treatment, in particular for PSC and IgG4 disease patients. Many patients require medical therapy with conventional bile acid sequestrants, but tolerability and lack of efficacy can be an issue [87]. Evidence-based second-line-therapies, such as rifampicin and oral opiate antagonists, exist but there are significant issues with side-effects in some patients [88,89]. The development of better second-line therapies with fewer side-effects, which can be used in more general clinical settings is a clinical need. Recent work has hypothesized that potential pruritogens accumulate in the circulation of cholestatic patients and activate sensory neurons. Studies suggest that lysophosphatidic acid (LPA) and autotaxin (the serum enzyme that converts lysophosphatidylcholine into LPA) may play a critical role in pruritus and may serve as potential targets for future therapeutic interventions [90]. There is also a phase 2 trial in progress, looking at the effect of an apical sodium-dependent bile acid transporter inhibitor (ASBTi) in combination with UDCA in patients with PBC with moderate to severe pruritus (NCT01904058).

UK-PBC national cohort data suggest that the penetrance of effective therapy for pruritus is lower than anticipated (unpublished data). The authors feel this may be a reflection of the complexity of treatment paradigms. “Treat and forget” approaches would offer real advantages for patient management. A group

of patients are refractory to medical therapy for pruritus and the need for novel therapies in this group is significant (transplantation being a costly and limited alternative approach). There are anecdotal reports and case series data to support the use of physical approaches to therapy, including the molecular adsorbent recirculating system (MARS) and naso-biliary drainage [91,92]. Combining data from three centres showed that MARS leads to a significant reduction in pruritus (visual analogue scale [VAS]: from 70.2 ± 4.8 to 20.1 ± 4.2 , $p < 0.001$) and VAS decreased by 72% immediately after treatment and the benefit was maintained in 51% of patients at 1-month post-treatment [93]. However, these approaches are expensive with only a limited evidence basis to date. “Dummy”-controlled trials are difficult to undertake in this patient group and therefore an alternative form of prospective evaluation, potentially in form of intervention registries, is required.

The other major symptom which impacts PBC patients (and to a lesser extent PSC and AIH, although less studied and reported), and has the greatest unmet clinical need with regard to symptoms, is fatigue with associated cognitive symptoms [94–96]. This appears to be the major contributing factor to quality of life impairment in some cohorts, and is a facet of clinical practice unresponsive to currently effective disease-modifying therapies, such as UDCA and liver transplantation [16,97]. It is notable that there may be a geographic variation with emerging unpublished data showing a North/South divide in the incidence of fatigue. The evidence regarding the underpinning mechanism is improving and although a clinical trial of rituximab for the treatment of fatigue in PBC is ongoing (NCT01904058), no licensed therapies are currently available in this area. Physiological markers of fatigue and cognitive impairment would enable the development of targeted therapy and an objective response to such therapies would be of significant utility. Fatigue in PSC appears less marked than in PBC, and cognitive impairment (outwith the specific situation of end-stage disease and hepatic encephalopathy) is unreported. This may reflect a true difference or a lack of investigation to the same degree as fatigue has been studied in PBC. Similarly in AIH and IgG4-RD, the problem of fatigue may be more significant than currently recognized, but it is also possible that the impact of fatigue in these conditions is directly related to inflammatory activity and/or the presence of advanced liver disease.

Trial design and delivery

The issues of trial design, and in particular acceptable and feasible markers of response, are the ones which are holding back therapeutics development in AILD. Given the typically benign nature of PBC in older patients, and the apparent effectiveness of UDCA in this group, it is unlikely that broad-based trials of novel therapies in unselected patients will be either feasible or appropriate in the future [98]. Trials of novel disease-modifying therapies in PBC are likely to take place in the setting of stratified populations, with agents being evaluated in identified high-risk patients [43]. The approach, which is typically adopted in current trials is identification of risk through failure to adequately respond to UDCA after one year of therapy, with the potential for wasted opportunity for enhanced therapy, whilst the year of therapy is being monitored. An alternative approach would be to identify enhanced risk stratification parameters at baseline including demographic factors (young age at presentation and

male gender), histological parameters (a re-evaluation of the significance of disease activity and inflammation in these terms is warranted; an approach supported by the findings from the budesonide trials), biochemical parameters and serological factors (PBC-specific anti-nuclear antibody [anti-gp210] and anti-centromere antibody) have been associated with increased risk of non-response to UDCA and worse outcome [99,100]. Markers of high clinical risk, used for enrolment into trials of enhanced therapy are at present limited to biochemical measures, with inconsistencies between proposed measures. The standardization of approaches would be of significant value. Ongoing second-line therapy trials are utilizing improvement in composite biochemical risk scores because of the lack of other validated disease response markers. There are practical issues of undertaking placebo-controlled trials to hard clinical end points in a disease, which is often only slowly progressive, even in high-risk patients [98]. Response biomarkers aligned to the nature of the disease process and acceptable to regulatory bodies to allow rapid approval of therapies without the need to undertake non-feasible long-term outcome studies would be of significant use in PBC. Histology should be reconsidered as an end point for trials in PBC, PSC, and AIH, particularly if novel markers of fibrosis (e.g. collagen proportionate area), or immunodiagnosics can be developed. Transient elastography (TE) measures liver stiffness as a surrogate marker of liver fibrosis and is well-established in the management of other chronic liver diseases [101,102]. The value of TE in PBC has recently been shown. Floreani *et al.* found that TE performs better than other non-invasive markers in PBC, with an area under receiver operating characteristic (AUROC) of 0.89 and 0.99 for METAVIR stage \geq F2 and F4 fibrosis, respectively [103]. The comparator group for non-invasive tests of fibrosis for this study did not, however, include the serum enhanced liver fibrosis assay (ELF), which itself has significant diagnostic utility for fibrosis in PBC [104]. A recent study found the cut-offs for \geq F2 and F4 fibrosis to be 8.8 and 16.9 kPa, respectively. TE was found to be superior to biochemical markers for the diagnosis of advanced fibrosis and cirrhosis and an increase of 2.1 kPa/year to be associated with an 8.4-fold increased risk of decompensation, transplantation, or death ($p < 0.0001$) [105]. The critical issue with these non-invasive markers of disease severity, and the area of unmet need, is the extent of their responsiveness to biological change, resulting from the actions of a therapy (the key issue in trial outcomes). Clearly, demonstrating this property is challenging without access to therapies proven to reverse or stop fibrosis. However, in order to allow us to answer the question definitively in the future, it would be logical to include these modalities in trials of novel prognostic therapies in PBC. TE, as with liver biopsy, has a role in the risk stratification of patients at randomization in therapeutic trials.

Issues with regard to trial design and delivery in PSC mirror those in PBC. There are, however, specific additional challenges. Better diagnostic tools are required, particularly for early disease detection, as a lack of clear-cut diagnostic markers in routine clinical practice complicate the design and delivery of clinical trials in what are very heterogeneous patient groups. Response biomarkers other than those involving classic biochemistry and histological assessment are required, akin to the needs in PBC. TE is also a valuable surrogate marker for fibrosis in PSC. A prospective study, comparing TE to liver biopsy, found cut-off values for \geq F2, and F4 fibrosis to be 8.6 and 14.4 kPa, respectively, with high diagnostic accuracy. The rate of increase in liver stiffness is

independently linked with patient outcomes [106]. Further validation studies are required, but TE will have a likely role in the future trial design for PSC as for PBC. In PSC, there is also a need for longitudinal studies, to better define the radiologic course of the disease (using repeated magnetic retrograde cholangiopancreatography [MRCP]) and the relationships with clinical outcomes. This approach may lead to the identification of new markers of disease progression for clinical trials.

The pioneering trials, which defined therapy in AIH, were controlled and were associated with a high mortality rate in the controls. Clearly placebo-controlled trials in AIH would now be unethical, making trial design for novel agents in comparison to the standard of care difficult because of the high level of efficacy of conventional therapy in population terms. As with PBC, a stratified approach with targeting trials at high-risk, unresponsive patients is likely to be the most productive approach, but will require definition, validation and acceptance by regulatory bodies of criteria for high-risk/treatment non-response. As with PBC, trials to death or transplant as the outcome-measure are unlikely to be feasible, necessitating the identification of response biomarkers.

Structured care delivery

In all four disease areas it is likely that care delivery structures, which have evolved little over the last 20 years, will limit the effective delivery of optimal care in the future. The limitations associated with existing care delivery models are likely to be further exposed by the challenge of delivering effective second-line therapies when these are licensed. The challenges of structured care delivery are shared between AILD and other rare diseases, but at present are pronounced, because unlike some rare diseases, current therapy is in fact relatively cheap and therefore AILD is relatively hidden on the health economic radar of hospitals and commissioners. We believe that optimal care in all AILDs, and the most effective use of emerging therapies, will be achieved using structured care approaches. Incentives to evolve such approaches may paradoxically come from the introduction of more expensive therapies. Currently there is evidence to suggest limitations in care for primary therapies. The universal use of UDCA as first-line therapy for all PBC patients represents the first stage in an emerging stratified approach to treatment. Data from the UK-PBC national cohort suggests that an important minority of PBC patients does not receive UDCA as primary therapy [16]. Confusing messages in the literature regarding efficacy of UDCA may have contributed to this. A clear and simple message of the universal use of UDCA needs to be propagated. More recent UK data also suggest that limitations in the reach of maintenance therapy with azathioprine may contribute to the poor long-term outcomes identified in younger presenting AIH patients [62].

The current clinical delivery models in PBC do not typically incorporate concepts of UDCA-response and non-response and there is only poor awareness of the importance of assessing response and consideration of second-line therapy amongst managing clinicians [107]. This means high-risk, non-responding patients are not being identified for evaluation, enhanced monitoring (appropriate, given their high risk of disease progression) or for participation in trials of second-line therapy. Development of a stratified care delivery model will clearly be necessary for targeting of second-line therapies once they reach clinical practice.

Review

The lack of utilisation of UDCA-response stratification in practice also means that opportunities to reduce the care costs of low-risk patients (UDCA-responders) through community rather than hospital care are lost. At present the stratification model is not in place for AIH but this is likely to evolve in the short-term.

In PSC, in the absence of a clearly proven effective primary therapy, systematisation of the approach to management relates largely on screening for cancer. Still, the definition of putative subgroups in PSC, e.g. early stage disease, which might adequately respond to and benefit from UDCA-treatment, remains an unmet need. In all three diseases, clarification of the optimal approach for non-invasive screening for cirrhosis, indicating the need for hepatocellular carcinoma (HCC) and varices screening, is needed. It is unclear how widespread is the awareness of IgG4-RD and its potential as a diagnostic tool in patients with obstructive cholestatic features and/or bile duct-associated mass lesions. This may significantly limit the reach of effective treatment.

In a setting where only a single approach to therapy exists for each of these diseases, a conventional approach around simply using first-line therapies as widely as possible is reasonable. This approach will not, however, provide the sophisticated level of treatment evolution that will be necessary in the future. As second-line therapies become available in PBC shortly, and in AIH in the future, it is needed to develop paradigms to identify patients who will benefit from such second-line therapy in a way that does not lead to unacceptable geographical variation in therapy reach. Autoimmune liver diseases, each of which is a common rare disease, all represent paradigms for the challenge of delivering effective therapy, using structured models in practice. Approaches developed in optimizing liver disease may have applicability well beyond this area, making AILD an important test bed for the management of therapy delivery.

Financial support

The UK-PBC Research Consortium is funded by the Medical Research Council and works with, and receives funding from, industrial partners working in the area of therapy in PBC, including Intercept and Lumena.

Conflict of interest

D.E.J. Jones has had research funding from Intercept and Lumena as part of the UK-PBC Consortium. In his capacity at Newcastle University he has done consultancy work with Novartis, Johnson & Johnson and Intercept. K. Lindor has worked as an unpaid advisor to Intercept and Lumena. G.M. Hirschfield has had research funding from Intercept and Lumena as a co-investigator for UK-PBC. He is also an investigator and does consultancy work for Intercept, Gilead, Falk, FFPharma, NGM Bio, GSK, Janssen and Lumena. A. Lohse, J.K. Dyson, and G. Webb have nothing to disclose.

Authors' contributions

JKD and DEJ developed the original concept. All authors contributed to the drafting of the manuscript and critiqued it. All have seen and approved the final version.

References

- [1] Metcalf JV, Mitchinson HC, Palmer JM, Jones DEJ, Bassendine MF, James OFW. Natural history of early primary biliary cirrhosis. *Lancet* 1996;348:1399–1402.
- [2] Turchany JM, Uibo R, Kivik T, Van de Water J, Prindiville T, Coppel RL, et al. A study of antimitochondrial antibodies in a random population in Estonia. *Am J Gastroenterol* 1997;92:124–126.
- [3] Shibata M, Onozuka Y, Morizane T, Koizumi H, Kawaguchi N, Miyakawa H, et al. Prevalence of antimitochondrial antibody in Japanese corporate workers in Kanagawa prefecture. *J Gastroenterol* 2004;39:255–259.
- [4] Cunha LM, Bittencourt PL, Abrantes-Lemos CP, Moreira A, Almeida D, Parana R, et al. Prevalence of non-organ-specific autoantibodies in a rural community from northeastern Brazil: a population-based study. *Hum Immunol* 2012;73:70–74.
- [5] Chazouilleres O, Wendum D, Serfaty L, Rosmorduc O, Poupon R. Long term outcome and response to therapy of primary biliary cirrhosis-autoimmune hepatitis overlap syndrome. *J Hepatol* 2006;44:400–406.
- [6] Gregorio G, Portmann B, Karani J, Harrison P, Donaldson P, Vergani D, et al. Autoimmune hepatitis/sclerosing cholangitis overlap syndrome in childhood: a 16 year prospective study. *Hepatology* 2001;33:544–553.
- [7] Boberg KM, Chapman RW, Hirschfield GM, Lohse AW, Manns MP, Schruppf E, et al. Overlap syndromes: the International Autoimmune Hepatitis Group (IAIHG) position statement on a controversial issue. *J Hepatol* 2011;54:374–385.
- [8] Czaja AJ, Manns MP, McFarlane IG, Hoofnagle JH. Autoimmune hepatitis: the investigational and clinical challenges. *Hepatology* 2000;31:1194–1200.
- [9] Czaja AJ. Autoimmune liver disease. *Curr Opin Gastroenterol* 2009;25:215–222.
- [10] Alvarez F, Berg PA, Bianchi FB, Bianchi L, Burroughs AK, Cancado EL, et al. International Autoimmune Hepatitis Group Report: review of criteria for diagnosis of autoimmune hepatitis. *J Hepatol* 1999;31:929–938.
- [11] Czaja AJ, Carpenter HA. Autoimmune hepatitis with incidental histologic features of bile duct injury. *Hepatology* 2001;34:659–665.
- [12] Czaja AJ, Muratori P, Muratori L, Carpenter HA, Bianchi FB. Diagnostic and therapeutic implications of bile duct injury in autoimmune hepatitis. *Liver Int* 2004;24:322–329.
- [13] Wiesner RH, LaRusso NF, Ludwig J, Dickson ER. Comparison of the clinicopathologic features of primary sclerosing cholangitis and primary biliary cirrhosis. *Gastroenterology* 1985;88:108–114.
- [14] Ludwig J, MacCarty RL, LaRusso NF, Krom RA, Wiesner RH. Intrahepatic cholangiectases and large-duct obliteration in primary sclerosing cholangitis. *Hepatology* 1986;6:560–568.
- [15] Boberg KM, Fausa O, Haaland T, Holter E, Mellbye OJ, Spurkland A, et al. Features of autoimmune hepatitis in primary sclerosing cholangitis: an evaluation of 114 primary sclerosing cholangitis patients according to a scoring system for the diagnosis of autoimmune hepatitis. *Hepatology* 1996;23:1369–1376.
- [16] Carbone M, Mells G, Pells G, Dawas MF, Newton JL, Heneghan M, et al. Sex and age are determinants of the clinical phenotype of primary biliary cirrhosis and response to ursodeoxycholic acid. *Gastroenterology* 2013;144:560–569.
- [17] Al-Mamari S, Djordjevic J, Halliday J, Chapman R. Improvement of serum alkaline phosphatase to <1.5 upper limit of normal predicts better outcome and reduced risk of cholangiocarcinoma in primary sclerosing cholangitis. *J Hepatol* 2012;58:329–334.
- [18] Broome U, Lofberg R, Veress B, Eriksson LS. Primary sclerosing cholangitis and ulcerative colitis: evidence for increased neoplastic potential. *Hepatology* 1997;22:1404–1408.
- [19] Razumilava N, Gores GJ, Lindor KD. Cancer surveillance in patients with primary sclerosing cholangitis. *Hepatology* 2011;54:1842–1852.
- [20] Le Pendu J, Marionneau S, Cailleau-Thomas A, Rocher J, Le Moullac-Vaidye B, Clement M. ABH and Lewis histo-blood group antigens in cancer. *APMIS* 2001;109:9–31.
- [21] Vestergaard EM, Hein HO, Meyer H, Grunnet N, Jorgensen J, Wolf H, et al. Reference values and biological variation for tumor marker CA 19-9 in serum for different Lewis and secretor genotypes and evaluation of secretor and Lewis genotyping in a Caucasian population. *Clin Chem* 1999;45:54–61.
- [22] Tempero MA, Uchida E, Takasaki H, Burnett DA, Steplewski Z, Pour PM. Relationship of carbohydrate antigen 19-9 and Lewis antigens in pancreatic cancer. *Cancer Res* 1987;47:5501–5503.
- [23] Orntoft TF, Vestergaard EM, Holmes E, Jakobsen JS, Grunnet N, Mortensen M, et al. Influence of Lewis alpha1-3/4-L-fucosyltransferase (FUT3) gene

- mutations on enzyme activity, erythrocyte phenotyping, and circulating tumor marker sialyl-Lewis a levels. *J Biol Chem* 1996;271:32260–32268.
- [24] Ong SL, Sachdeva A, Garcea G, Gravante G, Metcalfe MS, Lloyd DM, et al. Elevation of carbohydrate antigen 19.9 in benign hepatobiliary conditions and its correlation with serum bilirubin concentration. *Dig Dis Sci* 2008;53:3213–3217.
 - [25] Mann DV, Edwards R, Ho S, Lau WY, Glazer G. Elevated tumour marker CA19-9: clinical interpretation and influence of obstructive jaundice. *Eur J Surg Oncol* 2000;26:474–479.
 - [26] Metzger J, Negm AA, Plentz RR, Weismuller TJ, Wedemeyer J, Karlsen TH, et al. Urine proteomic analysis differentiates cholangiocarcinoma from primary sclerosing cholangitis and other benign biliary disorders. *Gut* 2013;62:122–130.
 - [27] Barr Fritcher EG, Kipp BR, Voss JS, Clayton AC, Lindor KD, Halling KC, et al. Primary sclerosing cholangitis patients with serial polysomy fluorescence in situ hybridization results are at increased risk of cholangiocarcinoma. *Am J Gastroenterol* 2011;106:2023–2028.
 - [28] Navaneethan U, Gutierrez NG, Venkatesh PG, Jegadeesan R, Zhang R, Jang S, et al. Lipidomic profiling of bile in distinguishing benign from malignant biliary strictures: a single-blinded pilot study. *Am J Gastroenterol* 2014;109:895–902.
 - [29] Czaja A. The management of autoimmune hepatitis beyond consensus guidelines. *Aliment Pharmacol Ther* 2013;38:343–364.
 - [30] Hamano H, Kawa S, Horiuchi A, Unno H, Furuya N, Akamatsu T, et al. High serum IgG4 concentrations in patients with sclerosing pancreatitis. *N Engl J Med* 2001;344:732–738.
 - [31] Deshpande V, Sainani NI, Chung RT, Pratt DS, Mentha G, Rubbia-Brandt L, et al. IgG4-associated cholangitis: a comparative histological and immunophenotypic study with primary sclerosing cholangitis on liver biopsy material. *Mod Pathol* 2009;22:1287–1295.
 - [32] Stone JHZY, Deshpande V. IgG4-related disease. *N Engl J Med* 2012;366:539–551.
 - [33] Deshpande V, Zen Y, Chan JK, Yi EE, Sato Y, Yoshino T, et al. Consensus statement on the pathology of IgG4-related disease. *Mod Pathol* 2012;25:1181–1192.
 - [34] Webster G, Pereira S, Chapman R. Autoimmune pancreatitis/IgG4-associated cholangitis and primary sclerosing cholangitis-overlapping or separate diseases. *J Hepatol* 2009;51:398–402.
 - [35] Boonstra K, Culver EL, de Buy Wenniger LM, van Heerde MJ, van Erpecum KJ, Poen AC, et al. Serum immunoglobulin G4 and immunoglobulin G1 for distinguishing immunoglobulin G4-associated cholangitis from primary sclerosing cholangitis. *Hepatology* 2014;59:1954–1963.
 - [36] Maillette de Buy Wenniger LJ, Doorenspleet ME, Klarenbeek PL, Verheij J, Baas F, Elferink RP, et al. Immunoglobulin G4+ clones identified by next-generation sequencing dominate the B cell receptor repertoire in immunoglobulin G4 associated cholangitis. *Hepatology* 2013;57:2390–2398.
 - [37] Trivedi PJ, Hirschfield GM. Treatment of autoimmune liver disease: current and future therapeutic options. *Ther Adv Chronic Dis* 2013;4:119–141.
 - [38] Kumagi T, Guindi M, Fisacher SE, Arenovich T, Abdalian R, Coltescu C, et al. Baseline ductopenia and treatment response predict long-term histological progression in primary biliary cirrhosis. *Am J Gastroenterol* 2010;105:2186–2194.
 - [39] Corpechot C, Carrat F, Bahr A, Chretien Y, Poupon RE, Poupon R. The effect of ursodeoxycholic acid therapy on the natural history of primary biliary cirrhosis. *Gastroenterology* 2005;128:297–303.
 - [40] Pares A, Caballeria L, Rodes J. Excellent long-term survival in patients with primary biliary cirrhosis and biochemical response to ursodeoxycholic acid. *Gastroenterology* 2006;130:715–720.
 - [41] Kuiper EMM, Hansen BE, De Vries RA, Den Ouden-Muller JW, Van Ditzhuijsen TJM, Haagsma EB, et al. Improved prognosis of patients with primary biliary cirrhosis that have a biochemical response to ursodeoxycholic acid. *Gastroenterology* 2009;136:1281–1287.
 - [42] Corpechot C, Abenavoli L, Rabahi N, Chretien Y, Andreani T, Johanet C, et al. Biochemical response to ursodeoxycholic acid and long-term prognosis in primary biliary cirrhosis. *Hepatology* 2008;48:871–877.
 - [43] Nevens F, Andreone P, Mazzella G, Strasser S, Bowlus C, Invernizzi P, et al. The first primary biliary cirrhosis (PBC) phase 3 trial in two decades—an international study of the FXR agonist Obeticholic Acid. *J Hepatol* 2014;S525–S526.
 - [44] Levy C, Peter JA, Nelson DR, Keach J, Petz J, Cabrera R, et al. Pilot study: fenofibrate for patients with primary biliary cirrhosis and an incomplete response to ursodeoxycholic acid. *Aliment Pharmacol Ther* 2011;33:235–242.
 - [45] Kowdley K, Luketic V, Jones D, Chapman R, Burroughs A, Hirschfield G, et al. The first new monotherapy therapeutic PBC study in a decade? An international study evaluating the farnesoid X receptor agonist obeticholic acid in PBC. *Hepatology* 2011;54:416A–417A.
 - [46] Iwasaki S, Tsuda K, Ueta H, Aono R, Ono M, Saibara T, et al. Bezaafibrate may have a beneficial effect in pre-cirrhotic primary biliary cirrhosis. *Hepatol Res* 1999;16:12–18.
 - [47] Yano K, Kato H, Morita S, Furukawa R. Long-term administration of bezafibrate on primary biliary cirrhosis. *Acta Hepatol Jpn* 2002;43:115–120.
 - [48] Yano K, Kato H, Morita S, Takahara O, Ishibashi H, Furukawa R. Is bezafibrate histologically effective for primary biliary cirrhosis. *Am J Gastroenterol* 2002;97:1075–1077.
 - [49] Angulo P, Jorgensen RA, Keach JC, Dickson ER, Smith C, Lindor KD. Oral budesonide in the treatment of patients with primary biliary cirrhosis with a suboptimal response to ursodeoxycholic acid. *Hepatology* 2000;31:318–323.
 - [50] Rautiainen H, Karkkainen P, Karvonen AL, Nurmi H, Pikkarainen P, Nuutinen H, et al. Budesonide combined with UDCA to improve liver histology in primary biliary cirrhosis: a three-year randomized trial. *Hepatology* 2005;41:747–752.
 - [51] Leuschner M, Maier KP, Schlichting J, Strahl S, Herrmann G, Dahm HH, et al. Oral budesonide and ursodeoxycholic acid for treatment of primary biliary cirrhosis: results of a prospective double-blind trial. *Gastroenterology* 1999;117:918–925.
 - [52] Beuers U, Hohenester S, de Buy Wenniger LJ, Kremer AE, Jansen PL, Elferink RP. The biliary HCO₃⁻ umbrella: a unifying hypothesis on pathogenetic and therapeutic aspects of fibrosing cholangiopathies. *Hepatology* 2010;52:1489–1496.
 - [53] Myers RP, Swain MG, Lee SS, Shaheen AAM, Burak KW. B-cell depletion with Rituximab in patients with primary biliary cirrhosis refractory to ursodeoxycholic acid. *Am J Gastroenterol* 2014;108:933–941.
 - [54] Hirschfield GM, Liu X, Xu C, Lu Y, Xie G, Lu Y, et al. Primary biliary cirrhosis associated with HLA, IL12A, and IL12RB2 variants. *N Engl J Med* 2009;360:2544–2555.
 - [55] Mells GF, Floyd JAB, Morley KI, Cordell HJ, Franklin CS, Shin S-Y, et al. Genome-wide association study identifies 13 additional susceptibility loci for primary biliary cirrhosis. *Nat Genet* 2011;43:329–332.
 - [56] Chapman RW. High-dose ursodeoxycholic acid in the treatment of primary sclerosing cholangitis: throwing the urso out with the bathwater? *Hepatology* 2009;50:671–673.
 - [57] Wunsch E, Trottier J, Milkiewicz M, Raszeja-Wyszomirska J, Hirschfield GM, Barbier O, et al. Prospective evaluation of ursodeoxycholic acid withdrawal in patients with primary sclerosing cholangitis. *Hepatology* 2014;60(3):931–940.
 - [58] Tabibian JH, Lindor KD. Ursodeoxycholic acid in primary sclerosing cholangitis: if withdrawal is bad, then administration is good (right?). *Hepatology* 2014;60:785–788.
 - [59] Lindor K, Kowdley K, Luketic V, Harrison M, McCashland T, Befeler Aea. High-dose ursodeoxycholic acid for the treatment of primary sclerosing cholangitis. *Hepatology* 2009;50:808–814.
 - [60] Gotthardt D, Rudolph G, Kloters-Plachky P, Kulaksiz H, Stiehl A. Endoscopic dilation of dominant stenoses in primary sclerosing cholangitis: outcome after long-term-treatment. *Gastrointest Endosc* 2010;71:527–534.
 - [61] Ghazale A, Chari ST. Optimising corticosteroid treatment for autoimmune pancreatitis. *Gut* 2007;56:1650–1652.
 - [62] Hoereldt B, McFarlane E, Dube A, Basumani P, Karajeh M, Campbell MJ, et al. Long-term outcomes of patients with autoimmune hepatitis managed at a non-transplant center. *Gastroenterology* 2011;140:1980–1989.
 - [63] Sockalingam S, Blank D, Abdelhamid N, Abbey SE, Hirschfield GM. Identifying opportunities to improve management of autoimmune hepatitis: evaluation of drug adherence and psychosocial factors. *J Hepatol* 2012;57:1299–1304.
 - [64] Manns MP, Woynarowski M, Kreisel W, Lurie Y, Rust C, Zuckerman E, et al. Budesonide induces remission more effectively than prednisone in a controlled trial of patients with autoimmune hepatitis. *Gastroenterology* 2010;139:1198–1206.
 - [65] Dhirapong A, Lleo A, Yang G-X, Tsuneyama K, Dunn R, Kehry M, et al. B-cell depletion therapy exacerbates murine primary biliary cirrhosis. *Hepatology* 2011;53:527–535.
 - [66] Tsuda M, Moritoki Y, Lian Z-X, Zhang W, Yoshida K, Wakabayashi K, et al. Biochemical and immunologic effects of Rituximab in patients with primary biliary cirrhosis and an incomplete response to ursodeoxycholic acid. *Hepatology* 2012;55:512–521.
 - [67] Jones DEJ. Pathogenesis of primary biliary cirrhosis. *Gut* 2007;56:1615–1624.

Review

- [68] Carbone M, Neuberger J. Liver transplantation in PBC and PSC: indications and disease recurrence. *Clin Res Hepatol Gastroenterol* 2011;35:446–454.
- [69] Liermann Garcia RF, Garcia C Evangelista, McMaster P, Neuberger J. Transplantation for primary biliary cirrhosis: retrospective analysis of 400 patients in a single centre. *Hepatology* 2001;33:22–27.
- [70] Carbone M, Neuberger J. Liver transplantation in PBC and PSC: indications and disease recurrence. *Clin Res Hepatol Gastroenterol* 2011;34:46–54.
- [71] Mendes F, Couto CA, Levy C. Recurrent and de novo autoimmune liver diseases. *Clin Liver Dis* 2011;15:859–878.
- [72] Tripathi D, Neuberger J. Autoimmune hepatitis and liver transplantation: indications, results, and management of recurrent disease. *Semin Liver Dis* 2009;29:286–289.
- [73] Jones DE, Watt FE, Metcalf JV, Bassendine MF, James OF. Familial primary biliary cirrhosis reassessed: a geographically-based population study. *J Hepatol* 1999;30:402–407.
- [74] Lazaridis KN, Juran BD, Boe GM, Slusser JP, de Andrade M, Homberger HA, et al. Increased prevalence of anti-mitochondrial antibodies in first-degree relatives of patients with primary biliary cirrhosis. *Hepatology* 2007;46:785–792.
- [75] Prince MI, Chetwynd A, Diggle P, Jarner M, Metcalf JV, James OFW. The geographical distribution of primary biliary cirrhosis in a well-defined cohort. *Hepatology* 2001;34:1083–1088.
- [76] Ala A, Stanca CM, Bu-Ghanim M, Ahmado I, Branch AD, Schiano TD, et al. Increased prevalence of primary biliary cirrhosis near Superfund waste sites. *Hepatology* 2006;43:525–531.
- [77] Corpechot C, Chretien Y, Chazouilleres O, Poupon R. Demographic, lifestyle, medical and familial factors associated with primary biliary cirrhosis. *J Hepatol* 2010;53:162–169.
- [78] Corpechot C, Gaouar F, Chretien Y, Johanet C, Chazouilleres O, Poupon R. Smoking as an independent risk factor of liver fibrosis in primary biliary cirrhosis. *J Hepatol* 2012;56:218–224.
- [79] Zein CO, Beatty K, Post AB, Logan L, Debanne S, McCullough AJ. Smoking and increased severity of hepatic fibrosis in primary biliary cirrhosis: a cross validated retrospective assessment. *Hepatology* 2006;44:1564–1571.
- [80] Gershwin ME, Selmi C, Worman HJ, Gold EB, Watnik M, Utts J, et al. Risk factors and comorbidities in primary biliary cirrhosis: a controlled interview-based study of 1032 patients. *Hepatology* 2005;42:1194–1202.
- [81] Varyani FK, West J, Card TR. An increased risk of urinary tract infection precedes development of primary biliary cirrhosis. *BMC Gastroenterol* 2011;11:95.
- [82] Liang Y, Yang Z, Zhong R. Smoking, family history and urinary tract infection are associated with primary biliary cirrhosis: a meta-analysis. *Hepatol Res* 2011;41:572–578.
- [83] Mells G, Pells G, Newton JL, Heneghan M, Neuberger JM, Day D, et al. The impact of primary biliary cirrhosis on perceived quality of life: the UK-PBC national study. *Hepatology* 2013;58:273–283.
- [84] Benito de Valle M, Rahman M, Lindkvist B, Björnsson E, Chapman R, Kalaitzakis E. Factors that reduce health-related quality of life in patients with primary sclerosing cholangitis. *Clin Gastroenterol Hepatol* 2012;10:769–775.
- [85] Schramm C, Wahl I, Weiler-Normann C, Voigt K, Wiegand C, Glaubke C, et al. Health-related quality of life, depression, and anxiety in patients with autoimmune hepatitis. *J Hepatol* 2014;60:618–624.
- [86] Jones EA, Bergasa NV. The pruritus of cholestasis. *Hepatology* 1999;29:1003–1004.
- [87] Beuers U, Boberg KM, Chazouilleres O, Jones DEJ, Olnvernizzi P, Lammert F, et al. EASL practice guidelines on management of cholestatic liver diseases. *J Hepatol* 2009;51:237–267.
- [88] Prince MI, Burt AD, Jones DEJ. Hepatitis and liver dysfunction with rifampicin therapy for pruritus in primary biliary cirrhosis. *Gut* 2002;50:436–439.
- [89] McRae CA, Prince MI, Hudson M, Day CP, James OFW, Jones DEJ. Pain as a complication of use of opiate antagonists for symptom control in cholestasis. *Gastroenterology* 2003;125:591–596.
- [90] Kremer AE, van Dijk R, Leckie P, Schaap FG, Kuiper EMM, Mettang T, et al. Serum autotaxin is increased in pruritus of cholestasis, but not of other origin and responds to therapeutic interventions. *Hepatology* 2012;56:1391–1400.
- [91] Leckie P, Tritto G, Mookerjee R, Davies N, Jones DEJ, Jalan R. “Out-patient” albumin dialysis for cholestatic patients with intractable itch. *Aliment Pharmacol Ther* 2012;35:696–704.
- [92] Hofmann AF, Huet PM. Nasobiliary drainage for cholestatic pruritus. *Hepatology* 2006;43:1170–1171.
- [93] Pares A, Herrera M, Aviles J, Sanz M, Mas A. Treatment of resistant pruritus from cholestasis with albumin dialysis: combined analysis of patients from three centers. *J Hepatol* 2010;53:307–312.
- [94] Goldblatt J, Taylor PJS, Lipman T, Prince M, Baragiotta M, Bassendine MF, et al. The true impact of fatigue in primary biliary cirrhosis: a population study. *Gastroenterology* 2002;122:1235–1241.
- [95] Newton JL, Hollingsworth KG, Taylor R, El-Sharkawy AM, Khan ZU, Pearce R, et al. Cognitive impairment in primary biliary cirrhosis: symptom impact and potential aetiology. *Hepatology* 2008;48:541–549.
- [96] Björnsson E, Simren M, Olsson R, Chapman RW. Fatigue in patients with primary sclerosing cholangitis. *Scand J Gastroenterol* 2004;39:961–968.
- [97] Mells G, Pells G, Newton JL, Heneghan M, Neuberger JM, Day D, et al. The impact of liver transplantation on the phenotype of primary biliary cirrhosis patients in the UK-PBC cohort. *J Hepatol* 2013;59(1):67–73.
- [98] Combes B. Reflections on therapeutic trials in primary biliary cirrhosis. *Hepatology* 2005;42:1009.
- [99] Nakamura M, Komori A, Ito M, Kondo H, Aiba Y, Migita K, et al. Predictive role of anti-gp210 and anticentromere antibodies in long-term outcome of primary biliary cirrhosis. *Hepatol Res* 2007;37:S412–S419.
- [100] Nakamura M, Kondo H, Mori T, Komori A, Matsuyama M, Ito M, et al. Anti-gp210 and anti-centromere antibodies are different risk factors for the progression of primary biliary cirrhosis. *Hepatology* 2007;45:118–127.
- [101] Castera L, Vergnol J, Foucher J, Le Bail B, Chanteloup E, Haaser M, et al. Prospective comparison of transient elastography, Fibrotest, APRI, and liver biopsy for the assessment of fibrosis in chronic hepatitis C. *Gastroenterology* 2005;128:343–350.
- [102] Friedrich-Rust M, Ong MF, Martens S, Sarrazin C, Bojunga J, Zeuzem S, et al. Performance of transient elastography for the staging of liver fibrosis: a meta-analysis. *Gastroenterology* 2008;134:960–974.
- [103] Floreani A, Cazzagon N, Martinez D, Cavalletto L, Baldo V, Chemello L. Performance and utility of transient elastography and noninvasive markers of liver fibrosis in primary biliary cirrhosis. *Dig Liver Dis* 2011;43:887–892.
- [104] Mayo M, Parkes J, Adams-Huet B, Combes B, Mills AS, Markin RS, et al. Prediction of clinical outcomes in primary biliary cirrhosis by serum enhanced liver fibrosis assay. *Hepatology* 2008;48:1549–1557.
- [105] Corpechot C, Carrat F, Poujol-Robert A, Gaouar F, Wendum D, Chazouilleres O, et al. Noninvasive elastography-based assessment of liver fibrosis progression and prognosis in primary biliary cirrhosis. *Hepatology* 2012;56:198–208.
- [106] Corpechot C, Gaouar F, El Naggar A, Kemgang A, Wendum D, Poupon R, et al. Baseline values and changes in liver stiffness measured by transient elastography are associated with severity of fibrosis and outcomes of patients with primary sclerosing cholangitis. *Gastroenterology* 2014;146:970–979, quiz e915–e976.
- [107] Bodenheimer HC, Jones DEJ, Peterson P, Rudell E. PBC management among clinicians: gaps in clinical competence and practice performance-survey findings. *J Hepatol* 2014:S201.